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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,095	MITCHELL ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-43 and 92-155* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-43 and 92-155* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 12 November 2004 in response to the Non-Final Office Action mailed 24 March 2004. Claims 25-91 were considered in the 24 March Office Action. Claims 44-91 were canceled and claims 92-155 were added in the 12 November Paper. Claims 25-43 and 92-155 are pending and under consideration.

Priority

Claims 1-24 were denied benefit of the parent applications because there is no support for a target binding domain limited to between 10 and 600 nucleotides in length in the parent applications. Applicant's amendment has reinstated claims 1-24 as newly added claims 92, 93, 100-106, 113-115, 122-126, 133-137, 144 and 145, respectively. In addition, Applicant has added new claims 94, 97, 107, 110, 116, 119, 127, 130, 138 and 141, which limit the target binding domain to between 15-500 nucleotides; new claims 95, 98, 108, 111, 117, 120, 128, 131, 139 and 142, which limit the target binding domain to between 15 and 411 nucleotides; and new claims 96, 99, 109, 112, 118, 121, 129, 132, 140 and 143, which limit the target binding domain to between 200-411 nucleotides.

With regard to the range "10-600", as discussed in the previous Office Action (beginning on page 2), because the parent applications teach that the binding domain should be "at least 15-30 nucleotides in length", the disclosures clearly do not support a range that includes a lower limit that is less than 15 (beginning on page 2). Therefore, claims 92, 93, 100-106, 113-115, 122-126, 133-137, 144 and 145 are not entitled to benefit of the parent applications.

With regard to the range 15-500 and 15-411, Applicant urges that support for the lower limit of 15 nucleotides can be found in, for example, parent application 08/766,354, now US Patent No. 6,013,487, at column 6, lines 36-37, which reads, "one or two binding domains of at least 15-30 nucleotides (and up to several hundred nucleotides or more)", and that support for the upper limits can be found in Example 11, which discloses a pre-trans-splicing molecule having a binding domain of 411 nucleotides (paragraph bridging pages 25-26 of the 12 November Paper).

However, even if the disclosure of a 411 nucleotide binding domain would adequately support an upper limit of 411 and 500 nucleotides, which it does not, there is no disclosure of a 411 nucleotide binding domain in the parent applications. Furthermore, given the teaching that the binding domain can be up to "several hundred nucleotides or more" the skilled artisan would not have viewed a disclosure of a species that is 411 nucleotides as a blaze mark defining a range that is bounded by an upper limit of 411 nucleotides, let alone 500 nucleotides. In other words, because the instant disclosure, and that of the parent applications, clearly teach that there is essentially no upper limit to the size of the binding domain, the skilled artisan would not have viewed the disclosure of a species within the range of several hundred nucleotides or more as supporting a range that does not exceed 411 nucleotides or 500 nucleotides.

Likewise, with regard to a binding domain wherein the lower limit is 200 nucleotides, recited in claims 96, 99, 109, 112, 118, 121, 129, 132, 140 and 143, Applicant points to page 93, lines 8-12 of the instant specification for support (page 94 of the substitute specification filed 4 October 2001). The passage reads, "[t]he observation that long binding domains increased the specificity of PTMs suggested that very long binding domains (>200 nt) could further enhance discrimination", and adequately supports a lower limit of 200 nucleotides. However, the

examiner cannot find this teaching in the parent applications; therefore, the lower limit does not enjoy the support of the priority filings.

Response to Amendment

Rejection of claims 44-91 is rendered moot by cancellation of the claims.

Claim Objections

Claims 37 and 39 stand objected to because of the following informalities: The second step in each of the claims is mislabeled step "d)". Applicant's response does not address this objection.

Double Patenting

Claims 25-27, 29-34 and 36-38 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 9-16, 18-21 23, 25 and 32-34 of U.S. Patent No. 6,013,487. Applicant has agreed to file a terminal disclaimer, if appropriate, once the other outstanding rejections are overcome.

Claims 25-33, 35 and 39-43 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7-13, 15, 25-30, 32 and 33 of U.S. Patent No. 6,083,702. Applicant has agreed to file a terminal disclaimer, if appropriate, once the other outstanding rejections are overcome.

Claim Rejections - 35 USC § 112

Rejection of claims 25-31and 36-42 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the amendments to the claims.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 94-99, 107-112, 116-121, 127-132 and 138-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of

the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

As described above, new claims 94, 97, 107, 110, 116, 119, 127, 130, 138 and 141 limit the target binding domain to between 15-500 nucleotides, new claims 95, 98, 108, 111, 117, 120, 128, 131, 139 and 142 limit the target binding domain to between 15 and 411 nucleotides and new claims 96, 99, 109, 112, 118, 121, 129, 132, 140 and 143 limit the target binding domain to between 200-411 nucleotides.

Applicant urges that support for the ranges can be found in a passage that reads "one or two binding domains of at least 15-30 nucleotides (and up to several hundred nucleotides or more)" and in Example 11 of the instant disclosure, which teaches a pre-trans-splicing molecule having a binding domain of 411 nucleotides (*Id.*).

However, given the teaching that the binding domain can be up to "several hundred nucleotides or more" the skilled artisan would not have viewed a disclosure of a species that is 411 nucleotides as a blaze mark defining a range that is bounded by an upper limit of 411 nucleotides, let alone 500 nucleotides. In other words, because the instant disclosure, and that of the parent applications, clearly teach that there is essentially no upper limit to the size of the binding domain, the skilled artisan would not have viewed the disclosure of a species within the range of several hundred nucleotides or more as supporting a range that does not exceed 411

nucleotides or 500 nucleotides. Thus, the limitation of the binding domain to a range bounded by an upper limit of 411 nucleotides or 500 nucleotides constitutes new matter.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 92, 93, 100-105, 113-115, 122-126, 133-137 and 144-155 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 9-16, 18-21 23, 25 and 32-34 of U.S. Patent No. 6,013,487 (hereinafter '487). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims 92, 93, 100, 101, 103, 105, 104, 113, 114, 115, 122, 123, 124, 125, 126, 133, 134, 135, 136, 137 and 144 recite the same limitations as claims 1, 9, 2, 3, 5, 10, 12, 11, 13, 18, 14, 15, 16, 19, 20, 21, 23, 25, 32, 34 and 33 of the '487 patent, respectively, except that the instant claims are further limited to a target binding domain that is between 10 and 600 nucleotides in length. Likewise, claims 146-155 recite the same limitations as patented claims 1,

9, 10, 12, 13, 18, 19, 20, 32 and 34, respectively, except that the instant claims are further limited to a target binding domain that is at least 15-30 and up to several hundred nucleotides in length.

In column 4, '487 patent teaches that the binding domains should be at least 15-30 nucleotides in length and up to several hundred nucleotides. The application also discloses a working example wherein the binding domain is 18 nucleotides (see especially Figure 6 and the caption thereto). Thus, the '487 patent teaches that it is desirable that the binding domain should be greater than 15-30 nucleotides and that a binding domain of 18 nucleotides is effective. Therefore, a binding domain having a length which falls within the range of 10-600 nucleotides, or greater than 15-30 nucleotides and up to several hundred nucleotides would have been obvious to the ordinary skilled artisan in possession of U.S. Patent No. 6,013,487.

Claims 102 and 145 limit the nucleic acid molecule of the claims from which they depend to comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the splice region. The claims as a whole would be obvious to one of ordinary skill in the art in view of the limitations of '487 claims 9, 21 or 22 and the teachings in column 4 of '487 which provide that incorporation of a "safety", which covers elements of the 3' and/or 5' splice site, prevents undesirable non-specific trans-splicing.

Thus, the invention of the instant claims 92, 93, 100-105, 113-115, 122-126, 133-137 and 144-155 is not patentably distinct from the claims of the '487 patent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 92, 94, 95, 101, 103, 105, 107, 108, 114, 116, 117, 123-125, 127, 128, 134-136, 138 and 139 are rejected under 35 U.S.C. 102(b) as being anticipated by Puttaraju *et al.* (1999) *Nat. Biotechnol.* 17:246-252 (previously made of record).

Claims 92, 101, 103, 105, 114, 123-125, 134-136 and 145 recite the same limitations as previously examined claims 1, 4, 6, 8, 11, 14-16, 19-21 and 24, respectively, which were rejected as anticipated Puttaraju *et al.* in the Office Action mailed 20 May 2003.

As stated in the previous Office Action, the claims are directed to a cell comprising a nucleic acid molecule wherein the nucleic acid molecule comprises: a) one or more target binding domains wherein said target binding domain is between 10 and 600 nucleotides in length; b) a 3' splice region comprising a branchpoint, a pyrimidine tract and a 3' splice acceptor site; c) a spacer region that separates the 3' splice region from the target binding domain; and d) nucleotide sequence to be trans-spliced, wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell; directed to a cell comprising a vector wherein the vector expresses the nucleic acid molecule; directed to a method of producing a chimeric RNA molecule in a cell comprising contacting a target pre-mRNA in the cell with the nucleic acid molecule; directed to the nucleic acid molecule further comprising a safety sequence comprising one or more complementary sequences that bind to one or both sides of the 3' splice site; and directed to an expression vector which express the nucleic acid molecule.

Puttaraju *et al.* teaches a nucleic acid molecule comprising a target binding domain 18 nucleotides in length, a 3' splice region comprising a branchpoint, a pyrimidine tract and a 3'

splice acceptor site, a spacer region that separates the 3' splice region from the target binding domain, and a nucleotide sequence to be trans-spliced (see especially Figure 1 and the caption thereto, and Table 1). In figure 2 and the caption thereto, Puttaraju *et al.* teaches that the specificity of trans-splicing is improved by the inclusion of a safety sequence. The nucleic acid molecule of Puttaraju *et al.* thus comprises all of the limitations of the nucleic acid molecules of the independent claims. In the second column on page 249, Puttaraju *et al.* teaches a cell comprising a vector which expresses the nucleic acid molecule, and in the section bridging pages 249 and 250, Puttaraju *et al.* teaches a method of producing a chimeric RNA molecule in a cell comprising contacting a target pre-mRNA in the cell with a nucleic acid molecule. Puttaraju *et al.* further teaches the nucleic acid molecule which further comprises sequences encoding a translatable protein product (i.e., lacZ; see especially the paragraph bridging pages 249 and 250 and Figure 6 and the caption thereto), and comprising a sequence encoding a toxin (see especially Figure 1 and the caption thereto).

Furthermore, the limitations of new claims 94, 95, 107, 108, 116, 117, 127, 128, 138 and 139 are the same as the previously examined claims except that the limit the target binding domain to 15-500 or 15-411 nucleotides, which is anticipated by the 18 nucleotide binding domain of as Puttaraju *et al.*

Claims 92-95, 97, 98, 101-108, 110, 111, 113-117, 119, 120, 123-128, 130, 131, 135-139, 141 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Mitchell (WO 97/22250; previously made of record).

Claims 92, 93, 101-106, 114, 115 123-126, 134, 135-137 and 145 recite the same limitations as previously examined claims 1, 2, 4-9, 11, 12, 14-17, 19, 20-22 and 24, respectively, which were rejected as anticipated Mitchell in the Office Action mailed 20 May 2003. As stated therein, Mitchell teaches a nucleic acid molecule comprising a target binding domain of at least 15-30 and up to several hundred nucleotides in length, a safety sequence, a 3' splice region comprising a branchpoint, a pyrimidine tract and a 3' splice acceptor site, a spacer region that separates the 3' splice region from the target binding domain, and a nucleotide sequence to be trans-spliced (see especially the legend for Figure 1 beginning on page 6). Mitchell further discloses a specific embodiment wherein the target binding domain is 18 nucleotides (see especially Figure 6 and the caption thereto). Furthermore, Mitchell teaches that the nucleic acid molecule can include a 5' splice sequence located downstream of the toxin gene, thus separated from the target binding domain (see especially page 11, lines 29-30, and page 12, lines 33-34). Thus, Mitchell teaches all of the limitations of the independent claims. Mitchell further teaches the nucleic acid molecule, which further comprise sequences encoding a translatable protein product, comprising a sequence encoding a toxin (see especially Example 1, beginning on page 14) and comprising a translational stop codon (see especially the second paragraph on page 11). The nucleic acid molecule further comprising a 5' splice sequence, and vector and host cell comprising said nucleic acid molecule, taught by Mitchell meet the limitations of claims 92, 93, 101-106, 114, 115 123-126, 134, 135-137 and 145.

Furthermore, the limitations of new claims 94, 95, 97, 98, 107, 108, 110, 111, 116, 117, 119, 120, 127, 128, 130, 131, 138, 139 141 and 142 are the same as the previously examined

claims except that the limit the target binding domain to 15-500 or 15-411 nucleotides, which is anticipated by the 18 nucleotide binding domain of Mitchell.

In the Remarks filed with the 12 November Paper, Applicant argues that Puttaraju *et al.* and Mitchell do not qualify as prior art because the claimed invention is disclosed in the priority applications. Specifically, Applicant argues, "U.S. 6,013,487 discloses 'a nucleic acid molecule comprising a target binding domain of at least 15-30 nucleotides (and up to several hundred nucleotides or more' (col. 6, lines 36-37). The specification clearly supports a nucleotide range encompassing the upper limit of 600 nucleotides, with the disclosure of 'up to several hundred nucleotides or more.' One of skill in the art would also clearly be able to recognize that the earlier application, from which the present application claims priority, would provide support for the lower limit of 10 nucleotides." Likewise, Applicant argues that the teaching of "up to several hundred nucleotides or more" supports the upper limits of 411 and 500 nucleotides (page 30 of the Remarks).

This argument has been fully considered but is not deemed persuasive. The range recited in the passage cited by applicant is open ended with respect to an upper limit and, therefore, does not support any specific upper limit as recited in the instant claims. With regard to the lower limit of 10 nucleotides, the teaching that the binding domain should be "at least 15 nucleotides" clearly teaches away from embodiments of less than 15 nucleotides and, therefore, does not support a lower limit of less than 15 nucleotides. Thus, the rejected claims are not entitled to claim benefit of the parent application and are, therefore, anticipated by the teachings of Puttaraju *et al.* and Mitchell.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

PRIMARY EXAMINER